

## Fatigue & Parkinson's Disease

**Gordon Campbell:** Well good morning. Can you hear me all? Well thank you for coming. There are plenty of seats up front here if you'd like to get closer. My name is Gordon Campbell. I'm a Neurology Nurse Practitioner and have been at the VA here 19 years. A long time. I'm delighted that you're here today. I'm often in the Parkinson's clinic at the VA. How many people here, just show of hands, are from OHSU. Three or four. So I work at the VA and often times we're rushed in the clinic, and we're trying to adjust your Parkinson's medications and we're examining how stiff you are and how slow you are and whether the medicines carry you from one dose to the next. That's all very important because that's what we're trained to do, but it doesn't really address some other symptoms that aren't driven so much by whether you're stiff or slow. They're the non-motor symptoms of Parkinson's disease. Fatigue is one of these. We often address it at the end of the clinic visit or not at all. Just because we're busy filling out all the computer generated clicks and things. I encourage you to talk to your Neurologist and providers about this at the end of the visit. If this prompts some questions in you about fatigue bring them up. Push them into the discussion, because otherwise it won't happen and people will continue to monitor the things that they've been trained to do about dopamine and wearing off and dyskinesia. That's true for all these non motor symptoms. So I'm delighted to have a chance to talk with you a little bit and have the kind of discussion that I like to have typically with families and patients with Parkinson's disease, but never do because we're racing along to get to the next patient, trying to deal with what we see as the most important problems, the motor symptoms. But they're not the things that put people in nursing care centers and that raise the cost of care for Parkinson's disease. Those are the non-motor, and I'll go through a list of them. But fatigue for some people is a huge problem. As you can see here the concept of fatigue varies depending on the society you're talking to and when you're talking about it. It begins to emerge for the first time in medical journals and literature back in the 1850's with industrial fatigue. Well you can think of all the industry that was starting in the society. Then you go to the 1950's and you look through the medical literature and this isn't just Parkinson's or Neurology. This is general and there are all these epidemics of fatigue. Well antibiotics are just emerging. Then you go into the nineties and chronic fatigue or yuppie flu starts to emerge. You wonder about what's happening there. People are understanding what fatigue is, then in 1995 cancer and HIV. There's a lot of literature in both those areas, robust research right now looking at fatigue in those two areas. Just in the last couple years we've started to look at it in Parkinson's disease. Fatigue as you know, it's a private experience. I mean you have it, but I can't check it. I can't check the tone in your leg and find out whether you're fatigued or check your posture or your gait speed and tell me... that doesn't tell me that you're fatigued. It's also not a very useful symptom to doctors. That's one of the reasons that the Neurologists don't focus in on it because it doesn't lead us to a diagnosis like "Oh I'm having crushing sub-sternal chest pain today." Well now there's a symptom I want to hear about, or "I'm having dyskinesia or dystonia in my foot." There's a symptom I can use because it allows me to move my medications in one way or the other. But to say "Doc I'm fatigued". Like that just opens up a huge list of possibilities and it's sort of overwhelming and it doesn't point to something specific so there's a bias built into the

medical provider not to pay attention to this. Then you know people can feel fatigued and then feel kind of like “oh maybe I’m just lazy” or... kind of dismiss themselves. Like “why am I... I used to be an active guy and now I’m lazy.” What’s going on there? There’s some kind of a moral judgment being passed. I would say that lots of people complain of fatigue, particularly older patients and they say for no particular reason, but in fact there’s always a reason. This is true in general medicine and Neurology and part of what you have to do is push forward. Now whether we have great therapies yet to deal with it, it’s another question. But there’s usually something that is driving the fatigue and just shouldn’t be dismissed as “well maybe I’m getting older”. So what is fatigue? Well it’s one of the most common symptoms if you look in general medicine primary care practice. It comes up right near the top of the list of things that drive people to come see their doctor. “I’m just tired all the time. I have a desire to rest. I don’t have any energy.” It can be chronic, and it can be acute. It may be mild. It may be incapacitating, quite variable. But there’s this sustained sense of exhaustion and decreased capacity not relieved by rest. This is critical for understanding what fatigue is. So it’s not sleepiness. Lots of medications including the Parkinson’s cause drowsiness. Sedation is a huge problem for a lot of our chronic medications for blood pressure, cardiac disease, bladder and bowel problems. They all work in the brain and they have their side effects in the brain. People are drowsy, but fatigue is not just drowsiness because when you take a nap you feel a little refreshed, but you don’t feel refreshed. Your fatigue is not lifted after a nap typically. That’s part of the definition of fatigue. It’s not just depression although it’s often associated with fatigue. It’s not just feeling cranky or hopeless. So it’s not relieved by rest and importantly it’s caused by usual and desired regular activities. We have a photo here of some marathon dancers. They’re fatigued, but that’s not the kind of fatigue we’re talking about. ...Normally doing and I’m just exhausted doing my regular stuff that I need to do to get by. Not some new exertion I picked up in the gym or some new class I took. It’s a big problem as I’ve mentioned here. In general medicine when you come in and say “Doc I’m just exhausted all the time.” Usually that points to a depression and more of a psychological flavor, although there are medical problems too. It’s a little different with Parkinson’s disease. A lot of people are fatigued that aren’t at all depressed or hopeless there. Feeling great about life, they just don’t have any gas in the tank. If you’re fatigued this creates problems for you. It’s probably a factor in maybe a third of our fatal car accidents. This data here is conflating fatigue and drowsiness a little bit here, but you can see how as you get more and more drowsy and more and more sort of inattentive your crash risk goes up substantially. You’ve heard the dopamine agonist causing sleep attacks and causing accidents at the wheel. “Gee I just fell asleep right at the red light Doc. I don’t know what happened. I wasn’t feeling tired before.” That’s drowsiness. Fatigue is more this sense of exhaustion. Again excessive daytime sleepiness, this drowsiness is different from fatigue and usually driven by some medical problem and I’ve mentioned here restless leg syndrome. Much more common in Parkinson’s disease is in the evening, and this is a circadian phenomenon, kind of a funny feeling in my legs, I kind of want to move them. Sort of a creepy crawly sensation, it’s hard to describe. If I get up and I pace around a little bit, walk downstairs, come back, I’m okay. But then it comes back when I lie down. It happens in the evening and it can disrupt sleep, make it hard for you to fall asleep, it can recur during the night. It’s very common in Parkinson’s disease. It has to do with problems of metabolism of iron

trafficking in and out of cells. Up in the same piece of real estate where Parkinson's disease also starts or is involved. So restless legs is common, obstructive sleep apnea, widely under recognized, very treatable narcolepsy. So people that are drowsy a lot need to look at their medication lists and a couple of these other symptoms and we think we know what depression is, but in the older male veteran I see that I really queue in on is "When you are doing something for fun does it still give you a kick?" If it doesn't, there's no real pleasure in it, I'm just going through the motion, that's a real red flag for me. Another one is I turn not to the patient, but to the spouse and I say, "How is it living with your husband now? Is he cranky? Short tempered? Irritable?" Often times those two questions... and I'm married too. Marriages are not always easy, but if you're not getting any pleasure in life and you're short tempered and irritable those symptoms really perk up nicely with low doses of these low depressant medications. Which generally aren't any drag at all on your Parkinson's symptoms. So there are different kinds of fatigue and this fellow has been at the gaming table longer, but we're not going to talk about his kind. When people try to theorize about it in general medicine practices they look at fatigue with depression and sleepiness and they do these Venn diagrams as they call them and it's very hard to do research in this area because there's so much overlap with depression and sleepiness. As they say many medical problems can cause fatigue so as you experience with Parkinson's disease make sure that you've been screened for Diabetes and that they've looked at your Thyroid blood test. Make sure that if you have congestive heart failure it's well compensated. There are good medications for that. It's probably one of the most successful advances in internal medicine over the last ten years, the treatment of congestive heart failure. It used to carry a death sentence within two years. Now people are living active lives. Rheumatological diseases, cancer, anemia... a simple blood test. So these are the things that are fairly easy to screen for. We can tune these up. There are lots of drugs. The anti-hypertensive medications, beta blockers, anti-histamines, all can cause the fatigue problems that I've listed here. So again make sure that your primary care doctor and your neurologist have done a screening for these sorts of things because these are relatively easy to take care of and they drive a lot of fatigue.

Now I mentioned at the start that there are these motor and non-motor symptoms of Parkinson's disease. If all you've got is a hammer then everything is a nail. If you're focusing totally on motor problems like tremor, like slowness, that's what the neurologist or the nurse practitioner is going to be finding when he or she examines you. But these other problems with drooling and constipation, sleep problems, apathy, fatigue, cognitive slowing... This is what puts people with Parkinson's in nursing homes. This is what quadruples the cost of care in Parkinson's disease. It's not tremor. It's not stiffness. Certainly postural problems, if we're talking about motor difficulties, drive falls, hip fractures, and institutionalization. Huge problem, but tremor doesn't put people in nursing homes. Slowness doesn't. It's these non-motor symptoms. "I just don't have any energy. I'm depressed. I'm apathetic. I'm constipated. So the medicines never get to the proximal illium. I can't absorb my Sinemet anymore. I don't turn on. I'm constipated." This is a non-motor symptom of Parkinson's disease. These don't typically respond to Sinemet and the dopamine kind of medications. They're not dopaminergic problems. Parkinson's disease doesn't just knock out one transmitter. It knocks out several. It doesn't just start in the substantia nigra. In the mid-brain it

actually starts down further in the brain stem in the medulla years before it actually affects higher up. Pathologists have found that it's a much more widespread disease in the brain and the brain stem than we appreciated five and ten years ago. So it's not just a dopamine deficiency and these non-motor symptoms reflect that. So if you're drooling and we give you more Sinemet that doesn't really help the drooling, or if you're apathetic it doesn't usually. It's always important whenever you have any symptom to reflect on the question "Gee when I take my Sinemet, or the dopamine agonist, does that symptom improve? Does the pain in my shoulder, that I thought was bursitis, does that get better with Sinemet?" Okay maybe that's a Parkinsonian/dopamine phenomenon. But if your problem doesn't get better with Sinemet dose and yet you find the tremors easing off and you're getting out of the chair a little more easily then that's a non-motor kind of problem, or else a non-neurologic problem. So you do a little bit of your diagnosis just by looking at a problem and saying "When I go through my dose cycles does it get better?" Now I've been going on for twenty minutes here and nobody has asked any questions. I know you're a very nice audience, but you can ask questions. So just raise your hand otherwise I'll just keep going.

**Question from audience:** For a constant pain in your shoulder, you try to sleep on one side and your side starts hurting after about five or ten minutes.

**Gordon Campbell:** Well that's probably not Parkinson's disease, although Parkinson's disease can certainly affect sleep and cause pain at night and disrupt nice restorative sleep. That sounds more like a joint problem, bursitis, something in the shoulder. These non-motor symptoms, they can precede by five and seven years the onset of tremor. So people can report that five or seven years before any tremor started they were thrashing at night, and tried to throttle their wife and were having these violent dreams uncharacteristically because that little piece of real estate deep in the brain stem was broken, was dying. REM behavioral sleep disorder. So this is a non-motor symptom that is sometimes tough on a marriage. "Why were you like that last night Jack? Well I don't remember anything. I was asleep." A nice mild mannered guy during the day. So this is a non-motor symptom that precedes the Parkinson's disease. There's no assessment tools for ... Now there is one and it's being widely used. It's like the UPDRS rating scale, but it's for non-motor symptoms. So there's research that's going to be done because we now have a tool to begin to look at some of this and quantitate it.

**Question from audience:** ... (Too quiet)

**Gordon Campbell:** So the question is "Can we figure out when your Parkinson's started?" Yeah there's some research tools that we're looking at; PET scans, there's intense research now on so called bio markers, looking at peoples loss of smell which usually precedes Parkinson's disease, or some other subtle problems in their cardiac activity. You know the Parkinson's effects your heart, it effects your gut. There are more neurons in your gut than in your spine. There's a lot of neurological activity relating to Parkinson's disease in the gut. So I think we'll find ways of picking up Parkinson's years before the tremors start and give our protective medications and slow the disease. But that whole phenomenon's over the horizon right now.

So let's talk a little more about fatigue in Parkinson's disease. Here's a study done in Scandinavia, an eight year study, a fairly large group of people. How commonly are they fatigued and it seems that this group of people maybe one in three had fatigue, but over one in two had it by the time they were eight years into Parkinson's disease. So it's more common, but not necessarily present as you have the disease longer and longer, but it does seem to relate to how badly you're impaired and whether you're depressed and whether you're sleeping well. It can come and go for about half of the people and it's persistent in the other half. It is common even if you're sleeping well and you're mood is up. So this is a civil war soldier in his fatigues. The sensation in Parkinson's of fatigue is everything takes an effort. So as I keep hammering it's different than depression. It can impair walking safety and balance, and it's the most bothersome part of Parkinson's in maybe one out of three people when we look at surveys and it certainly lowers the quality of life. It's not just the usual ups and downs that you have from day to day as your transmitter levels fluctuate. It can come on suddenly and never go away. It can remit. You're just too tired to do the normal things, and when you take a rest it doesn't remit. It can come on after a stressful event or a respiratory infection or out of the blue. It's a kind of a hard symptom to lock into. Now we're not projecting an image I wanted to show. In terms of the neurology and the wiring it can happen up both up in the brain and it can happen both in the peripheral nervous system. I've shown you a couple of examples of disease in both here. Parkinson's seems to be more of a central problem. Myasthenia-gravis is a common illness in older men. They have trouble with double vision, they can't look up, their lids droop, and they get exhausted just doing simple motions like reaching for a plate because they are weak proximally in the shoulders and hips and they can't quite get out of a chair. It's quite a common problem actually. That's more of a peripheral problem, post polio syndrome, peripheral problem, but Parkinson's has more to do with the circuit up there in the brain. Theorists about fatigue try to parse it out and they can make distinctions between mental fatigue, physical fatigue, and motivation. So it's not necessarily that it's all physical. But the general sense in Parkinson's is that it's physical fatigue as opposed to mental fatigue. Can't finish your Sudoku or you can't finish your book kind of thing. So how do we measure fatigue? We've talked about it, we've done drug studies to find cures. We have to be able to quantitate it. We have to be able to do science on this sort of thing. There's questionnaires and there's one specific for Parkinson's disease. There are others specific for cancer and HIV and I think it's important because it's not the same experience in each disease. The trouble (... cuts out for a second) ...how you've been feeling. There's a lot of bias built into that question. It's just sort of a weak tool and it's not very sensitive. We can do tapping quests and we have a speaker that I'll introduce in a minute that will talk a little bit about some of the ways we do that. We can hook up accelerometers onto your waist. We can do fancy brain scans and EMG's or the needle study looking for carpal tunnel. It turns out that those studies, the carpal tunnel like studies, are normal in Parkinson's disease. Your problem is not out in the nerves or the neuro-muscular junction. It's more proximal, up in the head here. We don't generally do spect scans looking for oxygen utilization in Parkinson's patients unless you're in a research study. So it's more of a clinical assessment. So we don't have a blood test. We don't have an assay or an X-ray that would tell us "Oh yeah, you're fatigued. I can see you've had

some damage here in this area of your brain. That explains it.” This is a little watch that people wear that are involved in a multiple sclerosis study of fatigue. People strap on the watch and then four times a day they are prompted with a little buzzer to say “How are you feeling?” and you write in there down here exactly how you are fatigued. So this overcomes some of the concerns about bias. “How have you been feeling over the last week?” You get more real time data assessment. Fatigue is maybe the number one problem in multiple sclerosis. It’s just disabling. You can’t work. Even though they are walking without a cane and they look pretty good. Then this is that accelerometer where you hook it onto your belt and you wear it all the time and it picks up the sense of whether you’re moving around the house, getting up and down. It give some overall data of just how physically active was this person over the last week. So we come up with the medication that might work. You could clip this onto your belt and wear it and use the watch and that would give us a measure of just how you’re doing.

I’ve asked a speaker to come in. A neuro-scientist: Dr. Dimitrova. Please come up. She’s going to talk to you about some research in Parkinson’s on fatigue that’s being done at OHSU.

**Dr. Dimitrova:** So I present to you the human motor control lab and the director of this lab is Dr. Lou. All we do is research, the main focus of which is fatigue in Parkinson’s patients. So from what we can tell so far of what you experience as fatigue, you know that’s offering an untreated symptom of the disease. Our studies are intended to find what is the cause, where it’s localized and if we can find some way to treat it. So we characterize motor symptoms like how quickly you move because one of the symptoms is slowness of movement. Also non-motor abnormalities like fatigue. We evaluate the effect of different treatments, one of which is the trans-cranial magnetic stimulation. That is a non-invasive method that is used for studies of brain and muscle function. We are trying to see if this helps fatigue in Parkinson’s disease. We also evaluate the effects of different drugs like Levodopa or Modafinil or surgeries in Parkinson’s disease. That is the setup of the trans-cranial magnetic stimulation. So it’s a magnetic field applied on the skull, un-invasively. All you hear is a click when the pulse gets to the skull. You may feel it as a slight tapping on the skull. Then through that we activate the muscle and we record the muscle activity. That’s how we evaluate the brain and muscle function and coordination. There’s another approach that we use for our evaluation of fatigue and that’s...(cuts out for a second at 28:06) ...you have to tap two keys on the keyboard and we record that as music, but then we analyze it for your typing frequency, how quickly you move from one key to another, and even within thirty seconds that frequency of tapping decrease and that’s the sign of fatigue. On the upper portion you see how a normal person without Parkinson’s disease has a high tapping frequency in this test. On the bottom is a Parkinson’s diseased patient that is in this case much slower. Another approach to evaluate fatigue is when we do another exercise, it is pulling on that handle with an upward twist movement and no matter how hard you try you can’t keep doing that for a long time. So even when you do that for only thirty seconds the force declines and that’s how your muscle and brain get fatigued. There is another approach that we use. This is a device that you grab and lift. We can measure the force that you pinch the sensor and the force you use to lift it. It can detect also tremor because the signal that we

get from there starts to be... this way. While with a normal person it goes up and stays flat. So this is some of our current studies. One of them is for the effect of the trans-cranial magnetic stimulation. So when you have that for ten minutes or twenty minutes and you do the exercises before and after that we can compare these and see if this has had some effect on fatigue and on your movement. Another study that we have going on focuses on mental fatigue because one problem is the physical fatigue that is due to brain and muscle activity, but another side of the fatigue is the mental one. That is whether you are able to focus for a long time to do something. Whether you are feeling like doing the things that you need to do, or you're generally tired and you don't feel like doing anything. This test the study uses an attention test that you see an arrow and you have to press left or right key depending on the direction of the arrow. It looks easy, but when you do that for fifteen minutes and start responding to these targets much slower and slower. We also evaluate the effect of Levodopa and acupuncture on fatigue in Parkinson's disease. This study involved evaluation of placebo effect, which is whether we see some improvement in fatigue just because you feel you're being helped or being treated for fatigue and not actually physically helped. This is my contact information. I can certainly answer any questions that you have right now. Or you can call me and email me about all the studies that we do.

**Question from audience:** Are you looking for participants?

**Dr. Dimitrova:** Yes, for all the studies. The description of our study is in the Parkinson's news letter, the news letter of the Parkinson's center of Oregon which is the purple one outside in the hall that describes the study. If you can call me I can certainly explain all the studies that we have. For most of the studies that we do we ask the patients to be off medication for the last twelve hours before the visit so that we can assess the fatigue without the effect of Levodopa or any other medication that you take for Parkinson's disease. We try to do all the studies in the morning so that you take your evening medication, sleep overnight and skip on your morning dose. Then come to the study, then you can take it. In some of the studies we also test healthy disease so we'll appreciate the participation of your spouses too.

**Question from audience:** So can we participate in all three at the same time?

**Dr. Dimitrova:** Yes, yes. There's nothing that is that much interventional that will effect one study...

**Question from audience:** ... (Too quiet)

**Dr. Dimitrova:** No, you have to come to the OHSU for the study visits. Some of them involve only two visits or three visits. The study with the trans-cranial magnetic stimulation is longitudinal so we would be looking for how fatigue develops over a year and a half. This study involves visits every six months for a year and a half.

**Gordon Campbell:** The medications have their side effects where they work. All medications have side effects. If they are biologically active you are going to get side

effects. If someone thinks he can give you medicine and you'll never know you're taking it, particularly in the age when people get Parkinson's disease, they are lying. The question is risk and benefit, is it worth the side effects?

**Comment from audience:** ... (too quiet)

**Gordon Campbell:** Let's move on here. Dr. Dimitrova will stay if you have specific questions. Thank her for coming. I want to make a pitch for joining clinical research studies. I think it really puts you involved in the disease. It gives you sort of a reason for having Parkinson's disease. Maybe something good will show of it. There's actually literature now on people that are enrolled in clinical trials. They do better. They are hospitalized less. They are more active. It gets you involved in a community of people, other researchers, you get to come to luncheons, and we fatten you and things like that. That's part of my reason to have Dr. Dimitrova come is to incite you guys to say "Hey let's go over to OHSU." You've got the contact information. Get involved. We have research studies. We're always giving you forms at the VA clinic. So I think this is not just good for us, but I think it's good for you guys too. You might want to make that appeal. So we've spoken a little about mental fatigue and I'll go quickly here because I want to have some time for general questions at the end here. And this can come and go independent of the physical fatigue. So if we look at what predicts physical fatigue in Parkinson's disease apart from disease duration and depression, we can do some tests of cardiovascular fitness. Where we'll ask people to get up and walk 25 feet and get back. We ask them to walk for six minutes. We check their blood pressure and their oxygen utilization. All those things are rather robust predictors. So the better shape you're in the better you're going to handle your fatigue. Being sixty is no time to be out of shape. Having Parkinson's disease is no time to be out of shape. So I'm a real sort of evangelist about exercise after working fifteen years with Parkinson's patients. Those people that are physically active, they do better because as you all know the medicines that honeymoon for five years, everything looks great. Then you begin to slope down. The medicines work less predictably, less effectively and you have to rely on non-pharmacological ways of getting by. That's the time you want to be in shape. It involves a whole lifestyle that is common sense, but bears repetition. Eating properly, sleeping properly, exercise, some kind of meaningful activity or volunteer work in your life so that you're not just there with yourself alone or your spouse. There's lots of benefits from exercise. In Alzheimer's the mice that are finding their way through the water maze that are physically fit outperform the mice that are given the best Alzheimer's medications we have right now. They find the platform first. So exercise works. The brain is a plastic organism. It reorganizes, it adapts. By exercising you foster that plasticity; that re-adaptation. You can imagine the benefits of weight bearing exercise for loading your bones and preventing hip fractures. Certainly a big problem in Parkinson's disease. Cardiovascular health. Strength training is really important and we think "Well I'll just go for my walk. That's great." If you pick one thing walking is great. But some kind of strength training is really important. And it may just be getting into and out of a chair everyday and trying to do it slowly with your arms across your elbow. Each time you take your Parkinson's medicines practice getting slowly in and out of the chair. Throw your shoulders back against the wall, put your head back and press. Get that neck thrown



back and strong so you have your... (cuts out for a sec 38:13) Then stretch out your hamstrings so that these don't get tight and you're not left with this stooped posture that is just driven by short tight hamstrings. So that's a stretching exercise you can do. Just have your legs out on the ottoman and lean forward. So these are things for flexibility and strength. It turns out that a seventy year old benefits about 70% payoff that a twenty year old benefits during strength training. So it's not too late. Particularly the shoulder girdle and the hip girdle. Really getting strong... Yes?

**Question from audience:** ... (too quiet)

**Gordon Campbell:** So the question is whether Parkinson's disease is a work related injury. Well we think that there is some sort of neuro-toxin, so called, some exposure in a person who has the right susceptibility genes. And they're exposed maybe at the right time in their life. We think MS is driven by some virus exposure, but there's a window of time in your life when you need to have that immune system exposed to that Epstein bar virus or something like it and you have to have the right set of susceptibility genes. It's very complicated. Manganese workers for instance, ore workers; a lot of them get movement disorders, but you take a hundred people with the same exposure and only a couple people get it. Clearly genetics have a lot to do with it. So work related Parkinson's is very rare. But ongoing epidemiology persists. It's very tricky stuff. It's very hard to show causation in epidemiologic studies. We thought that people taking estrogen, women taking estrogen was a home-run for Alzheimer's and heart disease, then we did the real good prospective controlled studies and we found that it was a bust. So epidemiologic studies that link Parkinson's with well water or rural living and that sort of thing, it's very weak data. It's suggestive, but not causative.

**Question from audience:** ... (too quiet)

**Gordon Campbell:** So the question is concerning Agent Orange and Parkinson's disease. All the time we hear about this and there's new data coming out about the Persian Gulf exposure. I think the Agent Orange literature is very dirty. I mean it's not good science. That has something to do with the records that were collected in Vietnam. I will say that combat veterans in World War II are twice as likely to get Parkinson's disease as non-combat veterans in World War II. There's pretty good data on that. So Agent Orange and Parkinson's; I haven't seen literature on that, but you'd certainly wonder... I'm not aware of studies on Parkinson's. Now let's go on a little bit more here. This is a nice reference here. I think it's a great book on nutrition. It's kind of focused on Parkinson's disease and it talks about some of the exercise and balance studies like Tai Chi that I think are important for you to try and get involved in. The important thing is to pick something that's fun and that maybe has some social payoff for you so it's not just drudgery. It's hard to start an exercise program in mid-life. If you get some payoffs and its fun it's a lot easier.

**Question from audience:** ... (too quiet)

**Gordon Campbell:** So the testimonial there is that you have to do it to believe it. Get help from your doctors here. We've talked about other causes of fatigue, keeping a diary. That may be helpful to you because the medicines that we give you, and I'll mention a couple here, they're not home runs. They're singles. They help a little bit and you want to know maybe 20, 30, 40% better? It's not going to turn the clock back six years, but that's the way you may have to find out when you come back in two months and you've got your Methylphenidate or your Ritalin prescription. If you've got some kind of little graph or diary that can help us guide this a little bit here. Occupational therapists are very good at suggesting adaptive equipment and ways to conserve your energy so you can ask for an OT or occupational therapy referral. Again this might have to be you guys saying this because the busy neurologist is not going to remember this. "I want to see the OT. I want some adaptive equipment or some suggestions on managing energy better." Medications for fatigue, again none of them are fabulous. If they were you know you'd be hearing about it. I think their first steps are the anti-depressants. They generally don't work. There's some studies of Bupropion here that works on a different problem; Chronic Fatigue Syndrome. But there's no data that the SSRI's like Fluoxetine Citalopram and such seem to lift fatigue in Parkinson's disease. They certainly work in depression very well. So Ritalin, Methylphenidate, very helpful in cancer fatigue in pretty high dosages. I use it fairly regularly in the Parkinson's clinic and I'm fairly quick to try it in low dosages. It doesn't lead to escalating dosages and Tachyphylaxis. But if you've got heart problems it's clearly a risk and you may have to get an EKG and have maybe even a treadmill test before I'm comfortable test giving it, but I think it's worth a try. If you're on it for two to four weeks you try a little bit higher dose and it doesn't work... okay. Good, but I think you should at least offer yourself the opportunity because it's been very successful in some people, but I think in most people the effects are modest. The dopamine agonists have only been studied a little bit. An old fashioned medication, Bromokryptine that we don't use much anymore and the Pergolide, these ergot dopamine agonists are a little bit of help. The Pergolide set is very small, it's uncontrolled. It's really not very strong data. Amantadine, Selegiline; there's no data suggesting those are particularly helpful. We've heard a couple comments on Modafonil here. I think it certainly improves alertness. It doesn't seem to help in a fairly good controlled study. In excessive sleepiness in Parkinson's disease. It was kind of disappointing. We've thought that since that's such a problem with sleep attacks, and with our medications. It was disappointing. But again that's group data. A lot of times you might be in that minority that would get a benefit. So in general I'm fairly eager to try new medications on people. Low dosages, close follow-up, if you have a spouse there particularly they can help tell when you're confused or having hallucinations at night and can report it to us right away. Because a lot of these medications, if they do cause problems, it's reversible. So what else might help? Sinemet of course. I've talked about whether a symptom improves or not with Sinemet. Dr. Dimitrova was talking about the fatigue study and how you can tap more quickly and sustain that activity longer. It turns out that the fatigue questionnaires with those same patients in those studies didn't bump. So it's this funny thing. They perform better in the laboratory, but in their self-report they are rating whether they have more energy to get to church (cuts out for a second 46:20) ...into change with Sinemet. It's always worth the trial and to look carefully at your fatigue level. Acupuncture early studies, you've heard about one here. Nothing

much published. I think we're actively looking at it. OHSU has this alternative medicine program, Orca mind. It's very robust. We're looking at lots of different things. We're trying to do the same kind of science with a lot of herbal preparations and things that we've been doing with conventional allopathic medications. There are certainly lots of medications that are promoted for fatigue. Generally if you go on the internet and as you know as sophisticated consumers, natural doesn't necessarily mean safe. There are a lot of fillers in these things that can be troublesome. You are much more likely to get confusion and side effects up in the brain since you have a brain that's degenerating from Parkinson's disease. So I'm very cautious about a lot of these things. Partly because you don't know what you're getting. There's no control. There's no FDA supervision of a lot of these products. You don't know if one batch to the next, one lot to the next, if you're getting the same medications. So lots of caution here. Certainly no scientific support for these energy drinks that you'll see widely promoted. I put down B12 here. Certainly if you have a documented B12 deficiency. I think that's often missed and very common particularly if you've had a gastrectomy or any kind of surgery like that in the past that might effect absorption of this vitamin. Vitamin B12 is widespread and causes lots of problems with balance and cognition and is easily treated and checked for. So it could be helpful and coenzyme q10 that's being intensely studied. The preliminary studies showed some help in motor symptoms. The dosages that are being studied now are 1200 to 2400 milligrams. I often see people in the clinic 100 milligrams a day. Just understand that you are taking a homeopathic dose. The trouble is the real dose costs thousands of dollars a year. It comes out of your pocket. I'm not saying it wouldn't necessarily work for fatigue, but so far we don't see evidence. There's some suggestion that it works in mitochondria, these fuel cells, the battery pack in our system, and it might help with fatigue. We just don't have data yet.

**Question from audience:** ...(too quiet)

**Gordon Campbell:** So the question is whether or not some sort kind of malabsorption syndrome could drive this. I think our understanding of a lot of nutritional deficits and deficiencies is just fragmentary right now. There's a lot of big pharma looking in here. There's not a lot of money. There's no incentive. You can't patent B6. So I think we've pretty meager data on malabsorption syndromes. Certainly celiac disease, 1% of the general population, we didn't even hear about it fifteen years ago. Now you see all sorts of people, young and old, who are finding out that they have this incredible deficiency that no one knew about. It effects their mood and there's big neurology involved with celiac disease. So I think there's more to come on that, but unfortunately our corporate is not setup to fund it.

**Question from audience:** So it seems as though we're taking these medications ... (too quiet)... so is there anything being done to find other delivery methods?

**Gordon Campbell:** Well there is now a patch that's just been approved. So we're looking at alternative delivery systems. The GI system, as I've said a couple times, is profoundly effected by Parkinson's disease. The longer it takes your Sinemet to get through the stomach and into the small bowel where it's absorbed, the less you're going

to absorb. So that's one of the benefits of exercise. You move your bowels more regularly. You keep well hydrated. You take fiber, prunes, you know the drill. You move things through your gut, you get them into the proximal illium here and you absorb them much better. You get them into the bloodstream and then they get up to the brain. The big hurdle is getting them through the gut and into the bloodstream. So gastroparesis is a big problem with diabetics and it's a big problem in Parkinson's disease.

**Question from audience:** Another thing with Sinemet is we've been told that eating smaller... (too quiet)

**Gordon Campbell:** Yeah. So each of you learns your own absorption system and hopefully is watching these issues and diet compete for transport with the amino acids and the levadopa.

**Question from audience:** ... (too quiet)

**Gordon Campbell:** So the question is whether dietary protein can help regenerate brain tissue. One of the big problems is the brain is sort of immunologically privileged, walled off area within the body. Blood doesn't get into the brain tissue. It circulates and feeds oxygen to it, but the brain is very secure. It's hard to get drugs into the brain. The big molecules, the proteins, these long chained fatty acids, and a lot of these things that we think are very important for rebuilding nerve cell membranes. A lot of the drugs that we'd like to give people we can't get into the brain, and that applies to the large amino acids that you have in your foods too. The only things that trickle into the brain are really small molecules like glucose.

**Question from audience:** ...(too quiet)

**Gordon Campbell:** Well the blood levels of the more common blood proteins like albumen are normal in Parkinson's. You know people with Parkinson's disease tend to lose weight over time. So I think there are some key issues about malabsorption that are subtle, but I think impact mortality and such. But right now it's not a protein deficiency state in the usual sense, at least early in the disease. So I'm not aware of literature there. Just want to mention briefly Parkinson's care-giving while we're talking about fatigue. This is another whole topic so I won't spend much time on it, but make sure you take care of yourselves. If you lose ground you both come down. So I'm recognizing that we're five minutes over. If you need to leave that's fine. I'm happy to stay a couple more minutes. Here's my last slide. There's just some take home points here. Make sure that if you have the problems with fatigue; no energy, you're not boosted by rest, you're doing your usual activities and just don't have any gas in the tank, at least for good portions of the day. Make sure that you've tuned up all your other medication; your general medics and medical problems. Look over your medications. Challenge the doctors, "Do I need this dose? Do I need this medication?" Lots of drugs have side effects up in the brain as I've said. So you get your tune-up. You optimize your Parkinson's disease medications. Work about diet, are you taking too much Sinemet? It's often that too much is actually less. If you're taking more than a gram or 1200mg of

Sinemet a day, that may be too much. So are you actually swimming against the current there? Look at that with your doctors closely. Make sure that the carbidopa portion of the levadopa/carbidopa is appropriate. We've come to some new understandings there. See your occupational therapy. Make sure you get physically active and get rest. Try to get that balance of that healthy lifestyle. Stay involved socially including clinical research projects as we've mentioned here. Try some fatigue medications, but do that vigorously, but under close supervision. Then often, perhaps stopping the medication after a month or six weeks and see. "Am I better or not?" These things are not, as I say, homeruns, but there might be a subtle improvement. You try it for a month and then you come back. You've been a wonderful audience. Thank you very much. I'll stay for some questions. Thank you very much.